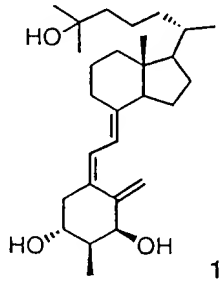
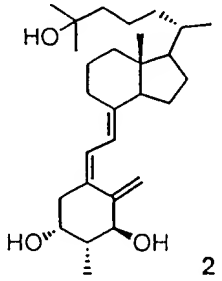
SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 2-METHYL-20-EPI ANALOGUES OF 1α,25-DIHYDROXYVITAMIN D_3. T. Fujishima, Z.-P. Liu, K. Konno and H. Takayama Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, JAPAN.

Active conformations of the A-ring of 1α,25-dihydroxyvitamin D_3 is still unclear. In order to investigate the conformation-activity relationship of the A-ring portion, we have synthesized the 2-methyl analogues of 1α,25-dihydroxyvitamin D_3, demonstrating that the introduction of the 2-methyl group elevates the affinity to the nuclear receptor (VDR) in some cases. In the present work, we designed and synthesized 2-methyl-20-epi analogues of 1α,25-dihydroxyvitamin D_3. The binding affinities of the synthesized compounds were preliminarily tested using the bovine thymus vitamin D receptor. The 2α-methyl-20-epi analogue (1) exhibited about ten-fold higher potency than 1α,25-dihydroxyvitamin D_3, whereas the 2β-methyl-20-epi analogue (2) had similar activity to 1α,25-dihydroxyvitamin D_3.



1



2

TENTH WORKSHOP ON VITAMIN D -- Strasbourg, France - May 24 - 29, 1997
ABSTRACT REPRODUCTION FORM (Instructions for preparing the abstract are given on the reverse side.)

Please indicate the category under which this abstract is submitted (check one only)

- ✓ (A) Free Communication (see opposite)
- ___ (B) Consideration for Young Investigator Travel Award as a Free Communication
- ___ (C) Invited Speaker/Plenary Presentation

FREE COMMUNICATIONS

- ___ (1) Consider for Oral Presentation (if not selected, the abstract will automatically be scheduled for a Poster Session)
- ✓ (2) Consider only for Poster Session

For an abstract submitted as a Free Communication, indicate below the one session you prefer for scheduling this abstract:

Basic Science Topics and Vitamin D

- ___ (a) Metabolites & analogs: pure chemistry
- ✓ (b) Chemistry: structure/function (interface with biology)
- ___ (c) Vitamin D/Analogs metabolism & catabolism
- ___ (d) $1,25(OH)_2D_3$ Receptors (biochemistry & molecular biology)
- ___ (e) Gene regulation by vitamin D steroids
- ___ (f) Retinoids & $1,25(OH)_2D_3$
- ___ (g) Rapid/Non-genomic actions
- ___ (h) Cell differentiation/Proliferation
- ___ (i) Transplantation/Immunology
- ___ (j) Brain, neural tissue
- ___ (k) Intestinal & renal actions
- ___ (l) Skin (actions)
- ___ (m) Bone, cartilage
- ___ (n) Muscle
- ___ (o) Calbindins-D and other Ca^{2+} binding protein
- ___ (p) Biological actions of vitamin D metabolites (other)
- ___ (q) Development & vitamin D
- ___ (r) Hormone secretion
- ___ (s) Hydroxylases (biochemistry & regulation)
- ___ (t) Evolutionary aspects
- ___ (u) Vitamin D-binding protein (DBP)
- ___ (v) Assay methodology (vitamin D & metabolites)
- ___ (w) Other (basic science topics)

Clinical Topics and Vitamin D

- ___ (x) $1,25(OH)_2D_3$ Receptor (VDR) polymorphisms
- ___ (y) Rickets & osteomalacia
- ___ (z) Osteoporosis
- ___ (za) Renal osteodystrophy
- ___ (zb) Cancer
- ___ (zc) Neonatology/Pregnancy/Development
- ___ (zd) Aging
- ___ (ze) Dermatology
- ___ (zf) Nutritional aspects
- ___ (zg) Other (clinical topics)

Type name and mailing address of submitting author:

Hiroaki Takayama
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, JAPAN
Tel.: (81) 426-85-3713 FAX: (81) 426-85-3714

Signature of submitting author: Hiroaki Takayama

INSTRUCTIONS FOR PREPARATION OF THE ABSTRACT

1. Abstract text must fit completely inside the indicated box.

2. If using a computer, do not use a font size that is smaller than 10. The font type should be Arial, Helvetica, Roman or Courier; do NOT use Italic or script styles. If you are using an electric typewriter, use ELITE type with a non-smudging ribbon. Only clean corrections will be accepted.

3. Be certain the TITLE IS COMPLETELY CAPITALIZED. The title should be followed by authors' names (initials or first name must precede the last name). Authors' names shall be continuously underlined. Department, institutional affiliation, city, country and postal zip code are required (do not include street address).

4. SINGLE SPACE all typing in the abstract. The text should be a single paragraph which starts with a three-space indentation.

5. When using abbreviations for compounds, spell them out in full when first mentioned, followed by the abbreviation in parentheses. Do not use "vitamin D" or "V-D" as a substitute/synonym for "$1\alpha,25(OH)_2D_3$"; they are chemically different compounds.

6. DO NOT ERASE. Remember that your abstract will appear exactly as you submit it; any erasure smudges, errors, misspellings, poor hyphenations and deviations from standard usage will be glaringly apparent in the published abstract.

7. If the abstract is submitted for consideration for a Young Investigator Travel Award (see Announcement for description), attach a letter from your supervisor or department head to testify as to your Young Investigator status (within 4 years of attainment of your professional degree).

8. DO NOT BEND ABSTRACT IN MAILING. Send, by airmail or by courier, the original typed copy of this abstract form plus fifteen (15) photocopies to:

   Tenth Workshop on Vitamin D
   Department of Biochemistry
   Boyce Hall, Room 5456
   University of California
   Riverside, CA 92521 USA

9. This abstract must be received by **Monday, February 10, 1997.** **FAX COPIES WILL NOT BE ACCEPTED.**

↑
deadline

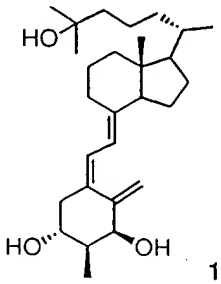
Example:

EXPRESSION OF THE CALBINDIN-D_{28K} GENE IS ACC
CHANGES IN CHROMATIN STRUCTURE. L. Brown and I
Biochemistry, University of Washington, Seattle, WA, USA 981

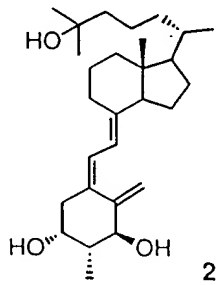
The chromatin structure of the chicken calbindin-D_{28K} and flanking DNA was studied in different chicken tissues. Expression of eukaryotic genes is accompanied by changes in the local structural organization of chromatin.

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 2-METHYL-20-EPI ANALOGUES OF 1α,25-DIHYDROXYVITAMIN D_3. T. Fujishima, Z.-P. Liu, K. Konno and H. Takayama Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, JAPAN.

Active conformation of the A-ring of 1α,25-dihydroxyvitamin D_3 is still unclear. In order to investigate the conformation-activity relationship of the A-ring portion, we have synthesized the 2-methyl analogues of 1α,25-dihydroxyvitamin D_3, demonstrating that the introduction of the 2-methyl group elevates the affinity to the nuclear receptor (VDR) in some cases (preceding abstract). In the present work, we designed and synthesized 2-methyl-20-epi analogues of 1α,25-dihydroxyvitamin D_3. The binding affinities of the synthesized compounds were preliminarily tested using the bovine thymus vitamin D receptor. The 2α-methyl-20-epi analogue (1) exhibited about ten-fold higher potency than 1α,25-dihydroxyvitamin D_3, whereas the 2β-methyl-20-epi analogue (2) had similar activity to 1α,25-dihydroxyvitamin D_3. Synthesis and biological evaluation of other stereoisomers of the 20-epi analogues will be presented.



1



2

TENTH WORKSHOP ON VITAMIN D -- Strasbourg, France - May 24 - 29, 1997
ABSTRACT REPRODUCTION FORM (Instructions for preparing the abstract are given on the reverse side.)

Please indicate the category under which this abstract is submitted (check one only)

- ✓ (A) Free Communication (see opposite)
- ___ (B) Consideration for Young Investigator Travel Award as a Free Communication
- ___ (C) Invited Speaker/Plenary Presentation

FREE COMMUNICATIONS
- ___ (1) Consider for Oral Presentation (if not selected, the abstract will automatically be scheduled for a Poster Session)
- ✓ (2) Consider only for Poster Session

For an abstract submitted as a Free Communication, indicate below the one session you prefer for scheduling this abstract:

Basic Science Topics and Vitamin D
- ___ (a) Metabolites & analogs: pure chemistry
- ✓ (b) Chemistry: structure/function (interface with biology)
- ___ (c) Vitamin D/Analogs metabolism & catabolism
- ___ (d) $1,25(OH)_2D_3$ Receptors (biochemistry & molecular biology)
- ___ (e) Gene regulation by vitamin D steroids
- ___ (f) Retinoids & $1,25(OH)_2D_3$
- ___ (g) Rapid/Non-genomic actions
- ___ (h) Cell differentiation/Proliferation
- ___ (i) Transplantation/Immunology
- ___ (j) Brain, neural tissue
- ___ (k) Intestinal & renal actions
- ___ (l) Skin (actions)
- ___ (m) Bone, cartilage
- ___ (n) Muscle
- ___ (o) Calbindins-D and other Ca^{2+} binding protein
- ___ (p) Biological actions of vitamin D metabolites (other)
- ___ (q) Development & vitamin D
- ___ (r) Hormone secretion
- ___ (s) Hydroxylases (biochemistry & regulation)
- ___ (t) Evolutionary aspects
- ___ (u) Vitamin D-binding protein (DBP)
- ___ (v) Assay methodology (vitamin D & metabolites)
- ___ (w) Other (basic science topics)

Clinical Topics and Vitamin D
- ___ (x) $1,25(OH)_2D_3$ Receptor (VDR) polymorphisms
- ___ (y) Rickets & osteomalacia
- ___ (z) Osteoporosis
- ___ (za) Renal osteodystrophy
- ___ (zb) Cancer
- ___ (zc) Neonatology/Pregnancy/Development
- ___ (zd) Aging
- ___ (ze) Dermatology
- ___ (zf) Nutritional aspects
- ___ (zg) Other (clinical topics)

Type name and mailing address of submitting author:
Hiroaki Takayama
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, JAPAN
Tel.: (81) 426-85-3713 FAX: (81) 426-85-3714
Signature of submitting author: